PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

14

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
FB/BM45376		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP00/01423	22/02/2000	24/02/1999
International Patent Classification (IPC) or national classification and IPC C12N15/31		
Applicant SMITHKLINE BEECHAM BIOLOGICALS S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
01/08/2000	10.04.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Roscoe, R Telephone No. +49 89 2399 2554

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP00/01423

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-59 as originally filed

Claims, No.:

1-17 as received on 23/03/2001 with letter of 23/03/2001

Drawings, sheets:

1/21-21/21 as originally filed

Sequence listing part of the description, pages:

1-9, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☒ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	15-17
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-17
Industrial applicability (IA)	Yes:	Claims	1-17
	No:	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

V. Reasoned statement on Novelty, Inventiv Step and Industrial Applicability

The documents mentioned in the present written opinion / International Preliminary Examination Report are numbered as in the search report, i.e. D1 corresponds to the first document of the search report etc.

- **Novelty (Art.33(2) PCT)**

D1 essentially discloses the nucleic acid and protein sequence of H. influenzae Rd "BASB070" - see SWISS-PROT: P45114 (gene HI1217). This is identified as a putative transferrin binding protein with similarity to TONB-dependent receptors. The probable location is suggested to be the outer membrane. The sequence corresponds to applicants BASB070 gene / protein. Further, there is a 89.88 % identity between this prior art sequence and Seq.ID No.4 of the present application in a 919 aa overlap. Anticipates claims 15-17. Other claims technically novel because relate e.g. to a vaccine composition.

D2 discloses cloning of the complete genome of H. influenzae Rd, including a reading frame which is 100% identical to seq. ID No.2 of the present application (i.e. HI1217). Basically same disclosure and relevance as D1.

- **Inventive Step (Art.33(3) PCT)**

The present application is based upon the fact that BASB070 has sequence characteristics of an outer membrane protein (OMP). The examples merely describe cloning of BASB070 into a bacterial expression vector. The results of this cloning are not even shown. Basically, applicant has taken a known gene, repeated computer-based sequence analysis by standard algorithms and has concluded as in the prior art that the BASB070 protein is an OMP. As a consequence, applicant claims uses relating to for example vaccination and diagnostic assays. However, it is obvious that an OMP is a potentially useful target or surface marker on a bacterial cell. There are hundreds of prior art documents which are based on this logic (see for example D2-D5). Further, isolation of a homolog from a similar strain is technically routine and suggested in e.g. D2, p.29. Applicant has not demonstrated any surprising feature of the

homolog (indeed as with the Rd-derived gene, no functions are tested). Hence, applicant has made no meaningful contribution to the art and the application is totally devoid of inventive subject-matter.
A problem-solution approach based on the vague problem identified on p.6, l.14-18 is not acceptable and seems to derive from applicants non-acknowledgement of the closest prior art documents D1 and D2. Viewing description on p.7, l.4-5, applicant implies that he has discovered that BASB070 has features of surface exposed molecule recognizable by immune system. The fact that the prior art had recognized this is not disclosed.

- **Industrial Applicability (Art.33(4) PCT)**

The present claims appear to have industrial applicability.

VIII. **Certain observations**

- **Clarity (Art.6 PCT)**

Where levels of identity are specified (i.e. claims 1-3, 5-8, 10-12), the length over which the identity is found needs to be specified. It is not acceptable to refer to extensive passage in description (p.46-51) to define terminology in the claims.

The meaning of the term "mimotope" needs to be clarified in the claims (claims 1, 14). Again, need to give more technical definition in claims, although clearly it would not be practical to introduce entire definition from description (p.29-31).

The terminology "immunologically active / immunogenic fragment / peptide" (claims 1-3, 5-9, 11, 12) is unclear in that even exceedingly small peptide fragments (which will undoubtedly be covered by the prior art) are included. This is especially unacceptable in claims where the use of the fragments is so broad (i.e. use as e.g. vaccine) as to be virtually non-limiting.

Claims

1. A vaccine composition comprising an effective amount of a polypeptide which polypeptide comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 2 or 4 or to an immunogenic fragment thereof, or which polypeptide comprises a mimotope of the said amino acid sequence or immunogenic fragment, together with a pharmaceutically acceptable carrier; wherein said immunogenic fragment (if necessary when coupled to a carrier) is capable of raising an immune response which recognises the polypeptide of SEQ ID NO: 2 or 4.

2. A vaccine composition according to claim 1 wherein the amino acid sequence has at least 95% identity to the amino acid sequence of SEQ ID NO: 2 or 4 or to an immunogenic fragment thereof, which (if necessary when coupled to a carrier) is capable of raising an immune response which recognises the polypeptide of SEQ ID NO: 2 or 4.

3. A vaccine composition comprising an effective amount of a polynucleotide which polynucleotide comprises a nucleotide sequence which has at least 85% identity to the nucleotide sequence of SEQ ID NO: 1 or 3 or to a fragment thereof which encodes an immunogenic polypeptide which (if necessary when coupled to a carrier) is capable of raising an immune response which recognises the polypeptide of SEQ ID NO: 2 or 4, together with a pharmaceutically acceptable carrier.

4. The vaccine composition according to any one of claims 1 to 3 wherein said composition comprises at least one other *Haemophilus influenzae* antigen.

5. An expression vector comprising an isolated polynucleotide which polynucleotide comprises a nucleotide sequence which has at least 85% identity to the nucleotide sequence of SEQ ID NO: 1 or 3 or to a fragment thereof that encodes an immunogenic polypeptide which (if necessary when coupled to a carrier) is capable of raising an immune response which recognises the polypeptide of SEQ ID NO: 2 or 4.

6. A recombinant live micro-organism comprising the expression vector of claim 5.

7. A host cell comprising the expression vector of claim 5 or a membrane of said host cell expressing an isolated polypeptide comprising an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 2 or 4, or to an immunogenic fragment thereof which (if necessary when coupled to a carrier) is capable of raising an immune response which recognises the polypeptide of SEQ ID NO: 2 or 4.

8. A process for producing a polypeptide comprising an amino acid sequence that has at least 85% identity to the amino acid sequence of SEQ ID NO: 2 or 4 or to an immunogenic fragment which (if necessary when coupled to a carrier) is capable of raising an immune response which recognises the polypeptide of SEQ ID NO: 2 or 4, comprising culturing a host cell of claim 7 under conditions sufficient for the production of said polypeptide and recovering the polypeptide from the culture medium.

9. A process for expressing a polynucleotide, which polynucleotide comprises a nucleotide sequence which has at least 85% identity to the nucleotide sequence of SEQ ID NO: 1 or 3 or to a fragment thereof that encodes an immunogenic polypeptide which (if necessary when coupled to a carrier) is capable of raising an immune response which recognises the polypeptide of SEQ ID NO: 2 or 4; the process comprising transforming a host cell with an expression vector comprising said polynucleotide and culturing said host cell under conditions sufficient for expression of said polynucleotide.

10. An antibody specific for the polypeptide of SEQ ID NO: 2 or 4 or an immunologically active fragment of the antibody which (if necessary when coupled to a carrier) is capable of raising an immune response which recognises the polypeptide of SEQ ID NO: 2 or 4.

11. A method of diagnosing a *Haemophilus influenzae* infection, comprising identifying a polypeptide which comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 2 or 4 or a fragment thereof, or an antibody that is specific for said polypeptide, present within a biological sample from an animal suspected of having such an infection.

12. Use of a composition comprising an immunologically effective amount of a polypeptide which comprises an amino acid sequence which has at least 85% identity to the amino acid sequence of SEQ ID NO: 2 or 4 or to an immunogenic fragment thereof, or which polypeptide comprises a mimotope of the said amino acid sequence of immunogenic fragment, in the preparation of a medicament for use in generating an immune response in a mammal, wherein said immunogenic fragment (if necessary when coupled to a carrier) is capable of raising an immune response which recognises the polypeptide of SEQ ID NO: 2 or 4.

13. Use of a composition comprising an immunologically effective amount of a polynucleotide which comprises a nucleotide sequence which has at least 85% identity to the nucleotide sequence of SEQ ID NO: 1 or 3 or to a fragment thereof that encodes am immunogenic polypeptide which (if necessary when coupled to a carrier) is capable of raising an immune response which recognises the polypeptide of SEQ ID NO: 2 or 4, in the preparation of a medicament for use in generating an immune response in a mammal.

14. A therapeutic composition useful in treating humans with *Haemophilus influenzae* disease comprising at least one antibody directed against the polypeptide of SEQ ID NO: 2 or 4 and a suitable pharmaceutical carrier.

15. An isolated polypeptide comprising the amino acid sequence of SEQ ID NO: 4 or an immunogenic fragment or mimotope thereof which (if necessary when coupled to a carrier) is capable of raising an immune response which recognises the polypeptide of SEQ ID NO: 2 or 4.

16. An isolated polynucleotide comprising a nucleotide sequence encoding the polypeptide of claim 15.

17. The polynucleotide of claim 16 comprising the nucleotide sequence of SEQ ID NO: 3 or a fragment thereof.